RESPONSE

Claims 1-6 and 8-31 are pending, claims 19-26 are withdrawn subject to a restriction requirement, and claims 1-6, 8-18, and 27-31 are rejected. Applicants have not amended, deleted, or added any claims. Accordingly, claims 1-6, 8-18, and 27-31 are presently being examined.

This application is a continuation-in-part of application serial no. 09/348,698, filed 7 July 1999, and a continuation-in-part of application serial no. 09/312,168, filed 14 May 1999.

In view of the following Response, applicants respectfully request that the Examiner reconsider and withdraw the rejections made in the outstanding Office Action.

Rejection of Claims 1-6, 8-17 and 31 under 35 U.S.C. Section 103(a) as being obvious over *Katz* in view of *Amschler et al.*

The Examiner has maintained the rejection of claims 1-6, 8-17 and 31 under 35 U.S.C. Section 103(a) as being obvious over United States patent no. 5,798,388 (*Katz*) in view of United States patent no. 5,449,676 (*Amschler et al.*). The Examiner states that *Katz* teaches a method of treating a disease state in mammals caused by mammalian cells involved in the inflammatory response which comprises contacting the mammalian cells involved in the inflammatory response with a therapeutically effective amount of an inflammatory mediator (col. 4, lines 58-67). The Examiner states that the inflammatory mediators are taught to be antioxidants selected from pyruvates (including lithium pyruvate, sodium pyruvate, potassium pyruvate, etc.) and pyruvate precursors, such as pyruvyl-glycene, pyruvyl-alanine, pyruvyl-leucine, pyruvyl-valine, etc. (col. 7, lines 21-41). The Examiner states that the inflammatory response reduced by the treatment is taught to be at least one of oxygen radical production, peroxide production, cytokine and/or protease production, prostaglandin production, erythema, histamine and interleukin production (col. 7, lines 15-20). The Examiner states that administration of the composition is in the form of liquids, ointments, etc. (col. 7, lines 52-56). The Examiner states that additional therapeutic agents, such as antibacterials, antivirals,

antifungals, antihistamines, proteins, enzymes, hormones, nonsteroidal anti-inflammatories, cytokines and steroids, are taught to be administered prior to, after and/or with the inflammatory mediator (col. 8, lines 13-18). The Examiner notes that while administration is taught for "injured cells" in general, the reference specifically teaches inhalation treatments for disorders such as bronchial asthma, bronchitis, etc. (col. 6, line 66; col. 7, line 10; col. 7, line 65; col. 8, line 12). The Examiner concedes that *Katz* does not specifically teach the administration of the composition to the nasal cells nor does *Katz* specifically teach the concentration of inflammatory mediator as herein claimed.

The Examiner argues that *Amschler et al.* teaches a method of treating inflammatory disorders of the lung (e.g. bronchitis, bronchial asthma, etc.) and inflammatory disorders of the nose (e.g. rhinitis, sinusitis, etc.) with an anti-inflammatory composition (col. 8, lines 36-57; col. 9, lines 61-68). The Examiner states that it would have been obvious to administer the composition of *Katz* to the nasal or sinus cavities for the treatment of inflammatory disorders of the nasal or sinus cavities, such as rhinitis or sinusitis because (1) *Katz* teaches the treatment of mammalian cells involved in a inflammatory response with an anti-inflammatory composition in general; (2) *Katz* teaches the treatment of inflammatory disorders such as bronchitis and bronchial asthma, specifically; and (3) *Amschler et al.* teaches that anti-inflammatory compositions are known in the art to treat inflammatory disorders of the nose, such as rhinitis and sinusitis, and that it is known in the art to treat inflammatory disorders of the lung in a similar manner to those of the nose. The Examiner concludes that one would have been motivated to treat inflammatory disorders of the nose in the manner disclosed by *Katz* (applicants assume the Examiner means *Amschler et al.*) because of an expectation of success in treating a specific inflammatory disorder in a manner taught to be beneficial, generally, by *Katz*.

The Examiner argues that it would have been obvious to utilize the concentration of inflammatory mediator in a formulation as instantly claimed because *Katz* teaches the administration in general and teaches that a formulation should comprise a therapeutically effective amount. Applicants traverse the Examiner's rejections.

The Examiner states that applicants argue that *Amschler et al.* may teach that 3-amino-6-arylpyridazine compounds may be used to treat inflammatory disorders

both in the lung and in the nose but *Amschler et al.* certainly does not teach that all compounds known to treat inflammatory disorders in the lung may be used in a similar manner to treat inflammatory disorders in the nose. The Examiner notes that *Katz* teaches a treatment of a disease state in a mammal caused by mammalian cells involved in the inflammatory response and there is no suggestion that this treatment is limited to the treating of inflammatory disorders of the lung. The Examiner argues that when examining the teaching of *Katz* with the teaching of *Amschler et al.*, that the inflammatory agents disclosed therein are known to be useful for both the treatment of inflammatory disorders of the lung and nose, the skilled artisan would have been motivated by an expectation of success in treating inflammatory disorders of the nose with the methods and compositions of *Katz*.

The Examiner further contends that applicant's arguments that *Amschler et al.* certainly does not teach that all compounds known to treat inflammatory disorders in the lung may be used in a similar manner to treat inflammatory disorders in the nose are not persuasive because the teachings of *Katz* are not limited to the treatment of inflammatory disorders of the lung.

In summary, applicants submit that treatment of inflammatory disorders in the lung is very different from the treatment of inflammatory disorders in the nose and sinuses because of the different cell types and routes of metabolism. In the sinuses, nitric oxide and hydrogen peroxide are produced by epithelial cells which produce 1000x more nitric oxide and hydrogen peroxide than that produced in lung cells. In the lungs, nitric oxide and hydrogen peroxide are produced by white blood cells and can be turned off, when not required, producing very little nitric oxide and hydrogen peroxide. In the sinuses, the production of nitric oxide and hydrogen peroxide is constant because these compounds are used to kill viruses and bacteria contained in the inhaled air. Thus the use of inflammatory mediators such as pyruvate or pyruvate precursors in the lungs and in the sinuses is quite different. In the lungs, excess pyruvate is transported into the cell and used as energy, to increase nitric oxide, protect mitochondria, protect cellular DNA, membranes and increase bronchial dilation. In the sinuses, excess pyruvate is used up in seconds by the very high concentrations of oxygen radicals. The main function of pyruvate and pyruvate precursors in the sinuses is to protect sinus medicines from destruction and to lower excess oxygen radicals. Applicants submit that the teachings concerning the synthetic 3-amino-6-arylpyridazine compounds of *Amschler et al.* are not

properly combinable with the natural pyruvate compounds taught by applicants because there is no suggestion or motivation in the references of *Katz* or *Amschler et al.* or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to the combine reference teachings in the manner proposed by the Examiner. At best, *Amschler et al.* may teach that 3-amino-6-arylpyridazine compounds may be used to treat inflammatory disorders both in the lung and in the nose but *Amschler et al.* certainly does not teach that ALL compounds known to treat inflammatory disorders in the lung may be used in a similar manner to treat inflammatory disorders in the nose.

The Examiner submits that the method of *Katz* is not limited to the treating of inflammatory disorders of the lung. Applicants submit, on the other hand, that *Katz* does not teach the treating of inflammatory disorders in the nose. It is not proper within the framework of Section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary for the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.

The present invention provides a method for treating a disease state in mammals caused by mammalian nasal and sinus cells involved in the inflammatory response. The method comprises contacting the mammalian nasal and sinus cells with an inflammatory mediator. The inflammatory mediator is present in an amount capable of reducing the undesired inflammatory response and is an antioxidant. The inflammatory mediator is selected from the group consisting of pyruvate and pyruvate precursors.

The present invention also provides a method for the treatment of rhinitis, eosinophilia syndrome, and sinusitis and related conditions associated with nasal congestion. The method comprises administering a nasal solution to the nostrils of a patient in need thereof. The nasal moisturizing saline solution comprises water; sodium chloride, 0.65% by weight; pyruvate, at least 0.1mM; buffer; and optionally a preservative. The nasal moisturizing saline solution is buffered and made isotonic.

The *Katz* reference discloses a method for treating asthma in mammals caused by mammalian cells involved in the inflammatory response. The method comprises contacting the mammalian cells with an inflammatory mediator. The inflammatory mediator is an antioxidant and is selected from the group consisting of

pyruvate and a pyruvate precursor. The inflammatory mediator is present in an amount capable of reducing the undesired inflammatory response and is not administered together with albuterol.

The *Amschler et al.* reference discloses 3-amino-6-arylpyridazine compounds that are said to be useful for the treatment of disorders of the bronchi, such as acute and chronic obstructive respiratory tract disorders of various etiologies including bronchitis, allergic bronchitis, and bronchial asthma (*Amschler et al.* at col. 8, lines 36-56), useful for the treatment of dermatoses (*Amschler et al.* at col. 9, lines 16-32), useful for the treatment of pathological states caused by certain cytokines (*Amschler et al.* at col. 9, lines 53-60), and useful for the treatment of allergic and/or chronic false reactions in the region of the upper respiratory tract (pharyngeal space, nose) and the adjoining regions (paranasal sinuses, eye) such as allergic rhinitis/sinusitis, chronic rhinitis/sinusitis, allergic conjunctivitis and nasal polyps (*Amschler et al.* at col. 9, lines 61-68).

To establish a *prima facie case* of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 706.02(j)

The initial burden is on the Examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972. 973 (Bd. Pat. App. & Inter. 1985). MPEP 706.02(j)

The Examiner states that "it is known in the art to treat inflammatory disorders of the lung in a similar manner to those of the nose" and cites *Amschler et*

al. to support this position. Applicants submit that the teachings concerning the synthetic 3-amino-6-arylpyridazine compounds of *Amschler et al.* are not properly combinable with the natural pyruvate compounds taught by applicants. Pyruvate is a combustion product of carbohydrates and forms the basic building block in the Krebs cycle. The synthetic 3-amino-6-arylpyridazine compounds of *Amschler et al.* are in no way not comparable to applicants' natural pyruvate compounds. In the lungs, excess pyruvate is transported into the cell and used as energy, to increase nitric oxide protect mitochondria, protect cellular DNA, membranes and increase bronchial dilation. In the sinuses, excess pyruvate is used up in seconds by the very high concentrations of oxygen radicals. There is no suggestion or motivation in the references of *Katz* or *Amschler et al.* or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to the combine reference teachings in the manner proposed by the Examiner. Moreover, there is no reasonable expectation of success combining *Katz* and *Amschler et al.* in the manner proposed by the Examiner. At best, *Amschler et al.* may teach that 3-amino-6-arylpyridazine compounds may be used to treat inflammatory disorders both in the lung and in the nose but *Amschler et al.* certainly does not teach that ALL compounds known to treat inflammatory disorders in the lung may be used in a similar manner to treat inflammatory disorders in the nose.

Accordingly, the Examiner's rejection of claims 1-6, 8-17 and 31 under 35 U.S.C. Section 103(a) as being obvious over *Katz* in view of *Amschler et al.* should be withdrawn.

Obviousness of a composition or process must be predicated on something more than it would be obvious "to try" the particular component recited in the claims or the possibility it will be considered in the future, having been neglected in the past. *Ex parte Argabright et al.* (POBA 1967) 161 U.S.P.Q. 703. There is usually an element of "obvious to try" in any research endeavor, since such research is not undertaken with complete blindness but with some semblance of a chance of success. "Obvious to try" is not a valid test of patentability. *In re Mercier* (CCPA 1975) 515 F2d 1161, 185 U.S.P.Q. 774; *Hybritech Inc. v. Monoclonal Antibodies. Inc.* (CAFC 1986) 802 F2d 1367, 231 U.S.P.Q. 81; *Ex parte Old* (BPAI 1985) 229 U.S.P.Q. 196; *In re Geiger* (CAFC 1987) 815 F2d 686, 2 U.S.P.Q.2d 1276. *In re Dow Chemical Co.* (CAFC 1988) F2d, 5 U.S.P.Q.2d 1529. Patentability determinations based on that as a test are contrary

to statute. *In re Antonie* (CCPA 1977) 559 F2d 618, 195 U.S.P.Q. 6; *In re Goodwin et al.* (CCPA 1978) 576 F2d 375, 198 U.S.P.Q. 1; *In re Tomlinson et al.* (CCPA 1966) 363 F2d 928, 150 U.S.P.Q. 623. A rejection based on the opinion of the Examiner that it would be "obvious to try the chemical used in the claimed process which imparted novelty to the process does not meet the requirement of the statute (35 U.S.C. 103) that the issue of obviousness be based on the subject matter as a whole. *In re Dien* (CCPA 1967) 371 F2d 886, 152 U.S.P.Q. 550; *In re Wiaains* (CCPA 1968) 397 F2d 356, 158 U.S.P.Q. 199; *In re Yates* (CCPA 1981) 663 F2d 1054, 211 U.S.P.Q. 1149. Arguing that mere routine experimentation was involved overlooks the second sentence of 35 U.S.C. Section 103. *In re Saether* (CCPA 1974) 492 F2d 849,181 U.S.P.Q. 36. The issue is whether the experimentation is within the teachings of the prior art. *In re Waymouth et al.* (CCPA 1974) 499 F2d 1273, 182 U.S.P.Q. 290. The fact that the prior art does not lead one skilled in the art to expect the process used to produce the claimed product would fail does not establish obviousness. *In re Dow Chem. Co.* (CAFC 1988) 5 U.S.P.Q.2d 1529.

Rejection of Claim 18 under 35 U.S.C. Section 103(a) as being unpatentable over *Katz* and *Amschler et al.* in further view of *Geria*

The Examiner has rejected claim 18 under 35 U.S.C. Section 103(a) as being unpatentable over *Katz* and *Amschler et al.* in further view of United States patent no. 5,478,565 (*Geria*). The Examiner concedes that *Katz* and *Amschler et al.* lack a specific teaching of oxymetazoline but that *Geria* teaches that oxymetazoline is known for the treatment of rhinitis and sinusitis, particularly with the congestion associated therewith (col. 4, lines 1-15). The Examiner argues that it would have been obvious to utilize oxymetazoline as the optional therapeutic agent of *Katz* because (1) *Katz* teaches that additional therapeutic agents may be utilized in addition to the inflammatory modulators disclosed therein; (2) the combined references render a treatment of rhinitis or sinusitis obvious; (3) oxymetazoline is taught by *Geria* as known in the art to be useful for the treatment of both rhinitis and sinusitis; and (4) it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.

The Examiner notes that the skilled artisan would have been further motivated to add the oxymetazoline to the treatment of the combined references because of an expectation of success of providing, in addition to the reduction of the inflammatory response effectuated by the inflammatory modulator of *Katz*, congestion relief to the patient suffering from sinusitis or rhinitis. Applicants traverse the Examiner's rejection.

The *Geria* reference discloses a topically applicable nasal composition capable of relieving mammalian sinus headache which comprises (i) an anaesthetically effective amount of an acid addition salt of dyclonine or pramoxine and (ii) an adrenergic ally effective amount of an acid addition salt of a sympathomimetic amine decongestant selected from the group consisting of an arylalkylamine, imidazoline and a cycloalkylamine incorporated in a pharmaceutically acceptable carrier. The sympathomimetic amine decongestant may be selected from the group consisting of phenylephrine, epinephrine, ephedrine, desoxyphedrine, phenylpropanolamine, tuaminoheptane, naphazoline, oxymetazoline, tetrahydrozoline, xylometazoline, propylhexadrine and mixtures thereof.

As set out above, the combination of the primary references of *Katz* and *Amschler et al.* do not provide applicants' method for treating a disease state in mammals caused by mammalian nasal and sinus cells involved in the inflammatory response. Because the primary references of *Katz* and *Amschler et al.* do not teach or suggest applicants' invention, the addition of the secondary reference of *Geria*, which merely discloses a topically applicable nasal composition containing a sympathomimetic amine decongestant which may be oxymetazoline, adds nothing to the primary references of *Katz* and *Amschler et al.*

Accordingly, the Examiner's rejection of claim 18 under 35 U.S.C. Section 103(a) as being unpatentable over *Katz* and *Amschler et al.* further in view of *Geria* should be withdrawn.

Rejection of Claims 27-30 under 35 U.S.C. Section 103(a) as being obvious over *Katz* and *Amschler et al.* and in further view of *Picciano*

The Examiner has rejected claims 27-30 under 35 U.S.C. Section 103(a) as being obvious over *Katz* and *Amschler et al.* and further in view of United States

patent no. 5,897,872 (*Picciano*). The Examiner states that *Katz* and *Amschler et al.* lack a specific teaching of the preferred solution formulation but that *Picciano* teaches the treatment of sinusitis with an isotonic buffered nasal saline solution comprising water, sodium chloride, 0.65% by weight, iodine, buffer and a preservative (col. 4, lines 52-59). The Examiner states that sodium bicarbonate, disodium phosphate/sodium phosphate and monobasic potassium phosphate/sodium hydroxide are taught as buffers (col. 4, lines 62-65) and phenylcarbinol, benzalkonium chloride and thimerosal are taught as preservatives (col. 4, lines 65-67). The Examiner states that the solution is taught to alleviate congestion and to provide moisturization (col. 4, lines 52-59). The Examiner concludes that it would have been obvious to treat a patient suffering from sinusitis with the inflammatory modulators of the combined references in the solution of *Picciano* because (1) *Katz* teaches the formulation of the compositions disclosed therein as formulated in solutions, in general; (2) the combined references render a method of treating sinusitis with inflammatory modulator compositions obvious; (3) *Picciano* teaches a solution which is itself useful for treating sinusitis; and (4) it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose The Examiner notes that the skilled artisan would have been further motivated to utilize the solution of *Picciano* as the solution for the administration of the inflammatory modulators of the combined references because of an expectation of success of providing, in addition to the reduction of the inflammatory response effectuated by the inflammatory modulator of *Katz*, both congestion relief and nasal moisturization to the patient suffering from sinusitis. Applicants traverse the Examiner's rejection.

The *Picciano* reference discloses a nasal moisturizing saline solution, comprising: a) water, b) sodium chloride, 0.65% by weight, c) iodine, at least 0.001 % by weight, d) buffer, and e) a preservative, wherein the nasal moisturizing saline solution is buffered and made isotonic.

As set out above, the combination of the primary references of *Katz* and *Amschler et al.* do not provide applicants' method for treating a disease state in mammals caused by mammalian nasal and sinus cells involved in the inflammatory response. Because the primary references of *Katz* and *Amschler et al.* do not teach or suggest applicants' invention, the addition of the secondary reference of

Picciano, which merely discloses a nasal moisturizing saline solution, adds nothing to the primary references of *Katz* and *Amschler et al.*

Accordingly, the Examiner's rejection of claims 27-30 under 35 U.S.C. Section 103(a) as being obvious over *Katz* and *Amschler et al.* and further in view of *Picciano* should be withdrawn.

The provisions of Section 103 must be followed realistically to develop the factual background against which the Section 103 determination must be made. It is not proper within the framework of Section 103 to pick and choose from anyone reference only so much of it as will support a given position to the exclusion of other parts necessary for the full appreciation of what such reference fairly suggests to one of ordinary skill in the art. The references of record fail to teach or suggest applicants' invention as a whole.

Applicants request the Examiner to telephone the undersigned attorney should the Examiner have any questions or comments which might be most expeditiously handled by a telephone conference. Applicants' attorney authorizes the Examiner to charge Deposit Account 13-4822 if there are any additional charges in connection with this Response.

In view of the foregoing Response, applicant requests allowance of the claims pending in this application. Applicant requests the Examiner to telephone the undersigned attorney should the Examiner have any questions or comments which might be most expeditiously handled by a telephone conference.

Applicant's attorney authorizes the Examiner to charge Deposit Account 13-4822 if there are any additional fees due in connection with this Response.

Respectfully submitted,
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